805. *Synthesis of Dihydronitidine.*

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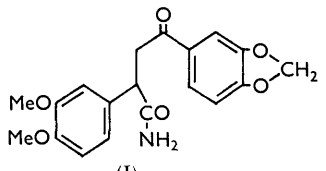
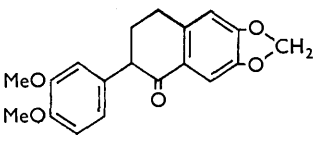
Two syntheses of dihydronitidine are reported, starting from the tetralone (II).

In a previous communication,[1] the single-step conversion of 2-aryl-1-tetralone oxime acetates into 9-methyl-1,2-benzophenanthridines was reported. During this study, it was found that the oxime acetate (III) gave a 40% yield of the 1,2-benzophenanthridine (IV). Meanwhile it was shown by Arthur, Hui, and Ng [2] that nitidine, a new alkaloid from *Zanthoxylum nitidum*, was 6,7-dimethoxy-10-methyl-2′,3′-methylenedioxy-1,2-benzophenanthridinium hydroxide, and we have confirmed this structure by two syntheses.

The tetralone (II) was prepared by the general method of Richardson, Robinson, and Seijo,[3] starting from acetopiperone and veratraldehyde. The amide [3] (I) was hydrolysed to the corresponding acid which was reduced by the Clemmensen method and then cyclised



(I)



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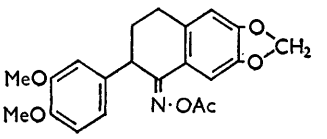
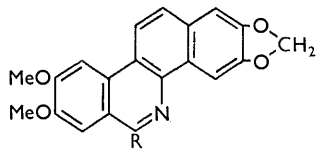
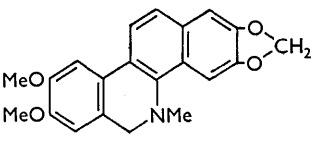


(III)



(IV); R = Me. (V); R = H



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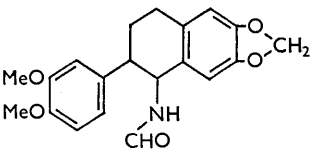

(VII)

to yield the tetralone (II). This was converted into the oxime, acetylated, and heated with acetic acid, acetic anhydride, and hydrogen chloride in a sealed tube, to yield the 9-methyl-1,2-benzophenanthridine (IV). In this connection, it is interesting that Schroeter [4] and Mills and Schofield [5] obtained the naphthylamines or their acyl derivatives from 1-tetralones and 1-phenyl-2-tetralones respectively. Our benzophenanthridine was formed by spontaneous cyclisation of the intermediate acetyl derivative and represents the first instance of a Morgan–Walls cyclisation proceeding without the use of conventional

[1] Gopinath, Govindachari, and Viswanathan, *Current Sci.* (*India*), 1959, **28**, 241.
[2] Arthur, Hui, and Ng, *Chem. and Ind.*, 1958, 1514.
[3] Richardson, Robinson, and Seijo, *J.*, 1937, 835.
[4] Schroeter, *Ber.*, 1930, **63**, 1308.
[5] Mills and Schofield, *J.*, 1956, 4213.

cyclisation reagents.[6] Oxidation of the compound (IV) with excess of selenium dioxide yielded the 9-carboxylic acid which was decarboxylated to give 6,7-dimethoxy-2′,3′-methylenedioxy-1,2-benzophenanthridine (V). This was converted into the methosulphate and reduced with zinc and hydrochloric acid to yield 9,10-dihydro-6,7-dimethoxy-10-methyl-2′,3′-methylenedioxy-1,2-benzophenanthridine (VI), identical (mixed m. p., ultraviolet and infrared spectra) with dihydronitidine.

The benzophenanthridine (V) was obtained in better overall yield from the tetralone (II) by the method of Bailey, Robinson, and Staunton.[7] By a Leuckart reaction, the tetralone yielded a separable mixture of 2-(3,4-dimethoxyphenyl)-3,4-dihydro-6,7-methylenedioxynaphthalene and the 1-formamido-derivative (VII). The former, on dehydrogenation, yielded 2-(3,4-dimethoxyphenyl)-6,7-methylenedioxynaphthalene, identified by its ultraviolet spectrum. The formamide was cyclised with phosphorus oxychloride in toluene to 3,4,11,12-tetrahydro-6,7-dimethoxy-2′,3′-methylenedioxy-1,2-benzophenanthridine which was dehydrogenated to the benzophenanthridine (V) and converted into dihydronitidine by the same steps as in the earlier method.

Experimental

α-(3,4-*Dimethoxyphenyl*)-γ-(3,4-*methylenedioxyphenyl*)-γ-*oxobutyronitrile*.—A stirred solution of 3,4-dimethoxy-3′,4′-methylenedioxychalkone [3] (10 g.) in 2-ethoxyethanol (65 ml.) containing acetic acid (2·5 ml.) was treated at 100°, during 3 min., with potassium cyanide (5 g.) in water (9 ml.). Heating was continued for a further 15 min. and water (100 ml.) was added, to give the nitrile (10 g.), m. p. 145—146°. (Richardson, Robinson, and Seijo [3] reported m. p. 144—146°. Their procedure offered difficulty for large-scale operations because of the sparing solubility of the chalkone in methanol and gave poorer yields of the nitrile.)

α-(3,4-*Dimethoxyphenyl*)-γ-(3,4-*methylenedioxyphenyl*)-γ-*oxobutyric Acid*.—The nitrile (5 g.) in acetic acid (35 ml.) was hydrolysed by concentrated sulphuric acid (5 ml.), in 15 min., to the amide [3] (5 g.), m. p. 178—180°. The amide (8 g.) was refluxed with alcohol (100 ml.) and 7% aqueous sodium hydroxide (100 ml.) for 8 hr. The solution was diluted with water (150 ml.) and extracted once with chloroform. The aqueous layer, on acidification, yielded the *acid* (7·5 g.), needles (from alcohol), m. p. 188—189° (Found: C, 64·0; H, 5·2. $C_{19}H_{18}O_7$ requires C, 63·7; H, 5·0%).

2-(3,4-*Dimethoxyphenyl*)-1,2,3,4-*tetrahydro*-6,7-*methylenedioxy*-1-*oxonaphthalene* (II).—The above keto-acid (10 g.), toluene (40 ml.), concentrated hydrochloric acid (53 ml.), zinc amalgam (24 g.), and 5% acetic acid (15 ml.) were refluxed for 48 hr., concentrated hydrochloric acid (10 ml.) being added every 10 hr. The toluene layer was separated, the aqueous layer was extracted once with benzene, and the combined toluene–benzene extracts were shaken with sodium carbonate solution. Acidification of the aqueous layer, followed by extraction with chloroform, gave α-(3,4-dimethoxyphenyl)-γ-(3,4-methylenedioxyphenyl)butyric acid (9 g.) as a pale yellow oil. This acid (2 g.) was heated with phosphorus oxychloride (5 ml.) at 100° for 15 min. and the red solution poured on ice. The product was extracted with chloroform, and the chloroform solution washed with sodium carbonate solution, then with water, dried (Na_2SO_4), and distilled. Chromatography of the residue in benzene over alumina gave the *tetralone* (0·8 g.), cubes (from dioxan–ethanol), m. p. 171—172° (Found: C, 70·1; H, 5·7. $C_{19}H_{18}O_5$ requires C, 69·9; H, 5·5%).

2-(3,4-*Dimethoxyphenyl*)-1,2,3,4-*tetrahydro*-1-*hydroxyimino*-6,7-*methylenedioxynaphthalene*.—The tetralone (1 g.), hydroxylamine hydrochloride (1 g.), and dry pyridine (5 ml.), heated at 100° for 5 hr. and poured into water, yielded the *oxime* (0·9 g.), needles [from benzene–light petroleum (b. p. 40—60°)], m. p. 170—171° (Found: C, 66·9; H, 5·6. $C_{19}H_{19}O_5N$ requires C, 66·9; H, 5·6%). The oxime (1 g.), heated at 100° for 3 hr. with acetic anhydride (2 ml.) and pyridine (2 ml.), yielded the *acetate* (0·9 g.), prismatic needles (from alcohol), m. p. 130—131° (Found: C, 65·8; H, 5·6. $C_{21}H_{21}O_6N$ requires C, 65·8; H, 5·5%).

6,7-*Dimethoxy*-9-*methyl*-2′,3′-*methylenedioxy*-1,2-*benzophenanthridine*.—A solution of the oxime acetate (0·4 g.) in acetic acid (2 ml.) and acetic anhydride (3 ml.) was saturated with dry hydrogen chloride at 0° and heated at 95—100° in a sealed tube for 8 hr., then treated with water. The yellow solid obtained was filtered off, washed with aqueous alcohol, and basified

[6] Theobald and Schofield, *Chem. Rev.*, 1950, **46**, 175.
[7] Bailey, Robinson, and Staunton, *J.*, 1950, 2277.

with ammonia, to yield the *benzophenanthridine* (0·15 g.), needles (from pyridine), m. p. 233°, $\lambda_{max.}$ 230, 275, 350, 365 mμ (log ε 4·50, 4·94, 3·67, 3·36), $\lambda_{infl.}$ 305, 330 mμ (log ε 4·43, 4·03) (Found: C, 72·7; H, 5·1. $C_{21}H_{17}O_4N$ requires C, 72·6; H, 4·9%).

6,7-*Dimethoxy*-2′,3′-*methylenedioxy*-1,2-*benzophenanthridine*.—The methylphenanthridine (0·4 g.) in ethyl acetate (80 ml.) was refluxed with selenium dioxide (0·4 g.) for 6 hr. and the solvent removed. The residue was extracted with pyridine, and the solvent distilled off. The product was treated with 50% acetic acid, and the brownish solid obtained was filtered off and dried, to give crude 6,7-dimethoxy-2′,3′-methylenedioxy-1,2-benzophenanthridine-9-carboxylic acid (0·15 g.). This was heated with copper bronze (0·2 g.) at 250—260° for 10 min., then cooled. Sublimation at 250—260°/0·03 mm. gave the *benzophenanthridine* (0·06 g.), needles (from pyridine–ethanol), m. p. 277—278°, $\lambda_{max.}$ 230, 275, 315, 370 mμ (log ε 4.56, 4·80, 4·38, 3·40), $\lambda_{infl.}$ 330, 347 mμ (log ε 4·11, 3·73) (Found: C, 72·1; H, 4·5. $C_{20}H_{15}O_4N$ requires C, 72·1; H, 4·5%).

Dihydronitidine.—A solution of the above benzophenanthridine (75 mg.) in xylene (2 ml.) and nitrobenzene (3 ml.) was boiled for a short time, and methyl sulphate (0·2 ml.) was added to the boiling solution. A yellow precipitate was rapidly formed and after 3 min. the solution was cooled and ether (10 ml.) added. The solid was collected and washed with ether, to yield the methosulphate (75 mg.), m. p. 307° (decomp.). A mixture of the methosulphate (70 mg.), zinc (5 g.), concentrated hydrochloric acid (8 ml.), and water (100 ml.) was refluxed for 3 hr., concentrated hydrochloric acid (2 ml.) being added every hour. The mixture was cooled and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and evaporated, to yield *dihydronitidine* (20 mg.), needles (from alcohol), m. p. 217—218°, undepressed by admixture with a sample of the natural product, $\lambda_{max.}$ 230, 280, 310 mμ (log ε 4·63, 4·59, 4·33) (Found: C, 71·8; H, 5·3. $C_{21}H_{19}O_4N$ requires C, 72·2; H, 5·4%).

2-(3,4-*Dimethoxyphenyl*)-1-*formamido*-1,2,3,4-*tetrahydro*-6,7-*methylenedioxynaphthalene*.—The tetralone (II) (2 g.) was heated under reflux at 180° for 3 hr. with formamide (5 ml.), formic acid (0·25 ml.), and ammonium sulphate (0·25 g.), formic acid (0·25 ml.) being added every 1 hr. The mixture was cooled, diluted with water, and extracted with chloroform. The dried (Na_2SO_4) chloroform extract gave, on removal of the solvent, a brownish gum which was chromatographed in benzene over alumina. The initial fractions of the eluate yielded, on evaporation, 2-(3,4-*dimethoxyphenyl*)-3,4-*dihydro*-6,7-*methylenedioxynaphthalene* (0·2 g.), needles (from methanol), m. p. 115—116°, $\lambda_{max.}$ 335 mμ (log ε 4·41) (Found: C, 73·5; H, 5·8. $C_{19}H_{18}O_4$ requires C, 73·5; H, 5·8%). Further elution of the column with benzene and finally with benzene containing 0·5% of ethanol yielded the *formamide* (0·9 g.), plates (from methanol), m. p. 187° (Found: C, 67·2; H, 5·6. $C_{20}H_{21}O_5N$ requires C, 67·6; H, 5·9%).

2-(3,4-*Dimethoxyphenyl*)-6,7-*methylenedioxynaphthalene*.—A mixture of the dihydronaphthalene (0·5 g.) and 30% palladised charcoal (0·2 g.) was heated at 240° for 30 min. in nitrogen. The mixture was cooled and extracted with chloroform, and the solvent removed. Crystallisation of the residue from ethanol gave 2-(3,4-*dimethoxyphenyl*)-6,7-*methylenedioxynaphthalene* (0·25 g.) as needles, m. p. 133°, $\lambda_{max.}$ 258, 297 mμ (log ε 4·65, 4·29) (Found: C, 74·3; H, 5·2. $C_{19}H_{16}O_4$ requires C, 74·0; H, 5·2%).

3,4,11,12-*Tetrahydro*-6,7-*dimethoxy*-2′,3′-*methylenedioxy*-1,2-*benzophenanthridine*.—The formamide (1 g.) in toluene (9 ml.) was refluxed gently for 30 min. with phosphorus oxychloride (3 ml.). The precipitated hydrochloride was filtered off, washed with ether, and basified with ammonia, to give the *tetrahydrobenzophenanthridine* (0·65 g.), needles (from pyridine–ethanol), m. p. 193—194°, $\lambda_{max.}$ 233, 287 mμ (log ε 4·67, 4·17) (Found: C, 71·3; H, 5·7. $C_{20}H_{19}O_4N$ requires C, 71·2; H, 5·6%).

6,7-*Dimethoxy*-2′,3′-*methylenedioxy*-1,2-*benzophenanthridine*.—The tetrahydrobenzophenanthridine (0·3 g.) was heated with 30% palladised charcoal (0·25 g.) at 230—240° for 30 min. in nitrogen. The product was repeatedly extracted with chloroform and the solvent evaporated. Crystallisation of the residue from pyridine–ethanol yielded the benzophenanthridine (0·15 g.), needles, m. p. and mixed m. p. with the previous specimen 277—278° (Found: C, 72·1; H, 4·5%).

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